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(71) *Sökande* / *Applicant (s)* — *AstraZeneca AB, Södertälje SE*

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PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

CHEMICAL COMPOUNDS

The present invention relates to novel compounds, and pharmaceutically acceptable salts thereof, which inhibit basic carboxypeptidases, more specifically carboxypeptidase U, and thus can be used in the prevention and treatment of diseases wherein inhibition of carboxypeptidase U is beneficial, such as thrombosis and hypercoagulability in blood and tissue. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

Fibrinolysis is the result of a series of enzymatic reactions resulting in the degradation of fibrin by plasmin. The activation of plasminogen is the central process in fibrinolysis. The cleavage of plasminogen to produce plasmin is accomplished by the plasminogen activators, tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Initial plasmin degradation of fibrin generates carboxy-terminal lysine residues that serve as high affinity binding sites for plasminogen. Since plasminogen bound to fibrin is much more readily activated to plasmin than free plasminogen this mechanism provides a positive feedback regulation of fibrinolysis.

One of the endogenous inhibitors to fibrinolysis is carboxypeptidase U (CPU). CPU is also known as plasma carboxypeptidase B, active thrombin activatable fibrinolysis inhibitor (TAFIa), carboxypeptidase R and inducible carboxypeptidase activity. CPU is formed during coagulation and fibrinolysis from its precursor proCPU by the action of proteolytic enzymes, such as thrombin, thrombin-thrombomodulin complex or plasmin. CPU cleaves basic amino acids at the carboxy-terminal of fibrin fragments. The loss of carboxy-terminal lysines and thereby of lysine binding sites for plasminogen then serves to inhibit fibrinolysis. By inhibiting the loss of lysine binding sites for plasminogen and thus increase the rate of plasmin formation, effective inhibitors of carboxypeptidase U are expected to facilitate fibrinolysis.

2-Mercaptomethyl-3-guanidinoethylthiopropanoic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Hendriks, D. *et al.*, Biochimica et Biophysica Acta, 1034 (1990) 86-92.

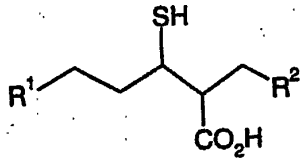
Guanidinoethylmercaptosuccinic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Eaton, D. L., *et al.*, The Journal of Biological Chemistry, 266 (1991) 21833-21838.

CPU inhibitors are disclosed in WO 00/66550 and WO 00/66557, and a pharmaceutical formulation containing a CPU inhibitor and a thrombin inhibitor is disclosed in WO 00/66152. Inhibitors of plasma carboxypeptidase B are disclosed in WO 01/19836.

Inhibitors of TAFIa are disclosed in WO 02/14285.

It has now been found that compounds of formula (I) are particularly effective as inhibitors of carboxypeptidase U and are thereby useful as medicaments for the treatment or prophylaxis of conditions wherein inhibition of carboxypeptidase U is beneficial.

Thus, the present invention provides a compound of formula (I):



(I)

wherein:

R^1 is phenyl {optionally substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano or hydroxy), C_{1-4} alkoxy, CF_3, OCF_3, methylenedioxy, $C(O)NH_2$, $S(O)_2NH_2$ or phenyl (itself optionally substituted by halogen)}, pyridinyl or tetrahydrothienyl;

R^2 is aminopyridinyl, aminothiazolyl or 3-azabicyclo[3.2.1]octyl;

provided that when R^1 is 6-aminopyridin-3-yl then R^2 is substituted phenyl, pyridinyl or tetrahydrothienyl;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

The compounds of formula (I) exist in isomeric forms and the present invention covers all such forms and mixtures thereof in all proportions. Both the pure enantiomers, racemic mixtures and equal and unequal mixtures of two enantiomers are within the scope of the present invention. It should also be understood that all the diastereomeric forms possible are within the scope of the invention.

The term C_{1-4} alkyl denotes a straight or branched alkyl group having 1 to 4 carbon atoms in the chain. Examples of alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

The term C_{1-4} alkoxy denotes an alkyl-O-group, where alkyl is straight or branched chain and exemples include methoxy and ethoxy.

Halogen includes fluoro, chloro, bromo and iodo (but is preferably fluoro or chloro).

In one particular aspect the present invention provides a compound of formula (I) wherein R^1 is phenyl {substituted (especially mono-substituted) by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano or hydroxy), C_{1-4} alkoxy (especially methoxy), CF_3 or methylenedioxy} or tetrahydrothienyl.

In a further aspect the present invention provides a compound of formula (I) wherein R^1 is phenyl {mono-substituted by halogen (especially chloro or fluoro), hydroxy, cyano, C_{1-4} alkyl (mono-substituted by cyano), CF_3 or methylenedioxy} or tetrahydrothienyl.

Aminopyridinyl is, for example, 6-aminopyridin-3-yl. Aminothiazolyl is, for example, 2-aminothiazol-5-yl. 3-Azabicyclo[3.2.1]octyl is, for example, 3-azabicyclo[3.2.1]oct-8-yl.

In a further aspect the present invention provides a compound of formula (I) wherein R^2 is aminopyridine (for example 6-aminopyridin-3-yl).

The compounds of the present invention can be prepared by adaptation of methods described in the literature (for example WO 00/66557), or by using or adapting Example 1 below. It will be appreciated that when adapting methods of the literature or Example 1 functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy, carboxylate and amino groups. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example tert-butyldimethylsilyl, tert-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, methoxymethyl, benzyloxymethyl and 4-methoxybenzyl. Suitable protecting groups for carboxylate include ethyl, tert-butyl and benzyl esters. Suitable protecting groups for amino include tert-butyloxycarbonyl, 2,4,6-trimethoxybenzyl and benzyloxycarbonyl. The use of protecting groups is described in 'Protective Groups in

Organic Synthesis', third edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999). The protective group may also be a polymer resin such as Wang resin or a 2-chorotrityl chloride resin.

The compounds of the invention are inhibitors of carboxypeptidase U and are thus expected to be useful in those conditions where inhibition of carboxypeptidase U is beneficial, such as in the treatment or prophylaxis of thrombosis and hypercoagulability in blood and tissues of mammals, such as man.

It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned include protein C resistance and inherited or aquired deficiences in antithrombin III, protein C, protein S and heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulatory and septic shock, circulating antiphospholipid antibodies, homocysteinemia, heparin induced thrombocytopenia and defects in fibrinolysis. The compounds of the invention are thus indicated both in the therapeutic and/or prophylactic treatment of these conditions. The compounds of the invention are further indicated in the treatment of conditions where there is an undesirable excess of proCPU/CPU.

Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis and pulmonary embolism, arterial thrombosis (for example in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis) and systemic embolism usually from the atrium during atrial fibrillation or from the left ventricle after transmural myocardial infarction.

Moreover, the compounds of the invention are expected to have utility in prophylaxis of re-occlusion and restenosis (that is, thrombosis) after thrombolysis, percutaneous trans-luminal intervention (PTI) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general.

Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism, fibrinolytic treatment when blood is in contact with foreign surfaces in the body, such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device, and fibrinolytic treatment when

blood is in contact with medical devices outside the body, such as during cardiovascular surgery using a heart-lung machine or in haemodialysis.

Furthermore, the compounds of the invention are expected to have utility in prophylaxis of atherosclerotic progression and transplant rejection in patients subject to organ transplantation, especially renal transplantation.

The compounds of the invention may also be combined and/or co-administered with any antithrombotic agent with a different mechanism of action, such as an anticoagulant (for example a vitamin K antagonist, an unfractionated or low molecular weight heparin, a synthetic heparin fragment such as fondaparinux, a thrombin inhibitor, a factor Xa inhibitor or other coagulation factor/enzyme inhibitor, a recombinant coagulation factor such as a recombinant human activated protein C) or an antiplatelet agent (such as acetylsalicylic acid, dipyridamole, ticlopidine, clopidogrel or other ADP-receptor [such as a P2Y12 or P2Y1] antagonist, a thromboxane receptor and/or synthetase inhibitor, a fibrinogen receptor antagonist, a prostacyclin mimetic or a phosphodiesterase inhibitor).

The compounds of the invention may further be combined and/or coadministered with thrombolytics such as tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), animal salivary gland plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction, ischaemic stroke and massive pulmonary embolism.

The compounds of the invention should have a selectivity for carboxypeptidase U over carboxypeptidase N of >100:1, preferably >1000:1, using the assay described below.

The inhibiting effect of the compounds of the present invention was estimated using the assay described in: Dirk Hendriks, Simon Scharpé and Marc van Sande, Clinical Chemistry, 31, 1936-1939 (1985); and Wei Wang, Dirk F. Hendriks, Simon S. Scharpé, The Journal of Biological Chemistry, 269, 15937-15944 (1994).

Thus, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present invention, the term "therapy" includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be understood accordingly.

The invention also provides a method of treating a condition where inhibition of carboxypeptidase U is beneficial in a mammal suffering from, or at risk of, said condition, which comprises administering to the mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically acceptable salts, solvates or solvates of salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound, salt, solvate or solvate of salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention thus also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

Also included in the invention are derivatives of compounds of formula (I) which have the biological function of compounds of formula (I), such as prodrugs. Prodrugs are, for example, (pivaloyloxy)methyl esters and [(ethoxycarbonyl)oxy]methyl esters of carboxylic acids.

The following Examples illustrate the invention.

EXAMPLES

General Experimental Procedures

Mass spectra were recorded on a VG Platform II mass spectrometer equipped with an electrospray interface (LC-MS). ^{1}H NMR measurements were performed on Varian UNITY plus 400, 500 and 600 spectrometers, operating at ^{1}H frequencies of 400, 500 and 600 MHz respectively. Chemical shifts are given in ppm with the solvent as internal standard. Chromatography separations were performed using Merck Silica gel 60 (0.063-0.200 mm).

The compounds named below were named using ACD/name version 4.55/ 03 July 2000 available from Advanced Chemistry Development Inc., Canada.

EXAMPLE 1

This Example illustrates the preparation of 2-[(6-aminopyridin-3-yl)methyl]-5-(1,1'-biphenyl-3-yl)-3-mercaptopentanoic acid

(a) 3-(1,1'-Biphenyl-3-yl)propanal

To a solution of 3-iodo-1,1'-biphenyl (0.964 g, 3.44 mmol) and tetrabutylammonium chloride (0.956g, 3.44 mmol) in dry DMF (3 mL) was added allyl alcohol (0.351 mL, 5.16 mmol), sodium hydrogencarbonate (0.723 g, 8.60 mmol), and palladium(II) acetate (31 mg, 0.14 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with EtOAc and the solid material filtered off (Celite). The filtrate was washed with water three times, dried (Na_2SO_4) and concentrated. Flash chromatography (heptan/*tert*-butyl methyl ether, 4:1) of the residue gave 3-(1,1'-biphenyl-3-yl)propanal (0.601 g, 83%).

(b) *tert*-Butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)pent-2-enoate

A solution of *tert*-butyl 3-{6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}-2-(diethoxyphosphoryl)propanoate (1.058 g, 2.31 mmol) in dry THF (4 mL) was added to a solution of sodium hydride (0.111 g, 60% in mineral oil, 2.77 mmol) in dry THF (3 mL) at 0 °C and the mixture was stirred at 0 °C for 60 min. To this mixture a solution of 3-(1,1'-

biphenyl-3-yl)propanal (0.582 g, 2.77 mmol) in dry THF (3 mL) was added, and the reaction mixture was allowed to attain room temperature over 22 h. EtOAc was then added, and the organic phase was washed with saturated aqueous NH_4Cl and water, dried (Na_2SO_4) and concentrated. Flash chromatography (toluene/EtOAc, 15:1) of the residue gave *tert*-butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)pent-2-enoate (1.105 g, 93%) as a mixture of E/Z-isomers.

(c) *tert*-Butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]pentanoate

A solution of 4-methoxy-α-toluenethiol (0.58 mL, 4.17 mmol) in dry, degassed DMF (2 mL) was treated at room temperature with a catalytic amount of sodium hydride (60% in mineral oil), followed by a solution of *tert*-butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)pent-2-enoate (1.073 g, 2.08 mmol) in dry, degassed DMF (5 mL). After 20 h at room temperature the reaction mixture was diluted with EtOAc and washed with water three times. The organic layer was dried (Na_2SO_4), concentrated, and subjected to flash chromatography (heptan/EtOAc, 3:1 and toluene/EtOAc 12:1) to give *tert*-butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]pentanoate (1.251 g, 90%)

(d) 2-[(6-Aminopyridin-3-yl)methyl]-5-(1,1'-biphenyl-3-yl)-3-mercaptopentanoic acid

tert-Butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]pentanoate (0.669 g, 1.00 mmol) was dissolved in trietylsilane (0.75 mL) and trifluoroacetic acid (6.0 mL). The solution was heated to 60 °C for 3h and then concentrated. Purification of the residue by reversed-phase HPLC (C-8 column, linear gradient 40%→100% of MeCN in 5% aqueous MeCN containing 0.15% trifluoroacetic acid) gave the title diastereomeric compound as the trifluoroacetic salt (0.342g, 68%) after freeze-drying. ^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 7.70 (dd, J = 2.1, 9.2 Hz, 0.5H), 7.66 (dd, J = 2.1, 9.2 Hz, 0.5 Hz), 7.61-7.58 (m, 2H), 7.53-7.51 (m, 1H), 7.46-7.41 (m, 4H), 7.38-7.32 (m, 2H), 7.22-7.16 (m, 1H), 6.88 (d, J = 9.1 Hz, 0.5H), 6.84 (d, J = 9.1 Hz, 0.5H), 3.10-2.74 (m, 6H) ,2.17-2.04 (m, 1H),1.91-1.78 (m, 1H). ^{13}C NMR (101 MHz, CD_3CN/D_2O): δ 175.3, 174.9, 153.0, 146.0, 145.8, 142.3, 141.1,140.9, 134.0,

133.9, 129.4, 129.2, 127.9, 127.9, 127.8, 127.3, 127.2, 127.1, 124.9, 124.8, 124.4, 124.1, 113.9, 113.8, 53.6, 53.0, 41.3, 40.5, 37.9, 33.1, 33.0, 31.2, 30.3. HRMS (ESI) calculated for $C_{23}H_{25}N_2O_2S$ 393.1637 $(M+H)^+$, found 393.1650.

EXAMPLE 2

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-6-phenylhexanoic acid was synthesised according to the procedure for Example 1, starting from 4-phenylbutanal.

EXAMPLE 3

2-[(6-aminopyridin-3-yl)methyl]-5-(3-cyanophenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 4

5-[3-(aminocarbonyl)phenyl]-2-[(6-aminopyridin-3-yl)methyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from 3-iodo-*N*-(2,4,6-trimethoxybenzyl)benzamide. 3-iodo-*N*-(2,4,6-trimethoxybenzyl)benzamide was synthesised from 3-iodobenzoic acid using standard procedures.

EXAMPLE 5

2-[(6-aminopyridin-3-yl)methyl]-5-[2-fluoro-4-(trifluoromethyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 6

2-[(6-aminopyridin-3-yl)methyl]-5-(3-chlorophenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 7

2-[(6-aminopyridin-3-yl)methyl]-5-(1,3-benzodioxol-5-yl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 8

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-pyridin-2-ylpentanoic acid was synthesised according to the procedure for Example 1, starting from 3-pyridin-2-ylpropanal.

EXAMPLE 9

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-(3,4,5-trimethoxyphenyl)pentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 10

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-pyridin-3-ylpentanoic acid was synthesised according to the procedure for Example 1, starting from 3-pyridin-3-ylpropanal.

EXAMPLE 11

2-[(6-aminopyridin-3-yl)methyl]-5-[4-(cyanomethyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 12

2-[(6-aminopyridin-3-yl)methyl]-5-(2-hydroxyphenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from 1-iodo-2-[(4-methoxybenzyl)oxy]benzene. 1-iodo-2-[(4-methoxybenzyl)oxy]benzene was synthesised from 2-iodophenol using standard procedures.

EXAMPLE 12

2-[(6-aminopyridin-3-yl)methyl]-5-[4-(aminosulfonyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from 4-iodo-*N*-(2,4,6-trimethoxybenzyl)benzenesulfonamide. 4-iodo-*N*-(2,4,6-trimethoxybenzyl)benzenesulfonamide was synthesised from 4-iodobenzenesulfonyl chloride using standard procedures.

EXAMPLE 13

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-(4-methoxyphenyl)pentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 14

2-[(6-aminopyridin-3-yl)methyl]-5-(4-hydroxyphenyl)-3-mercaptopentanoic acid was synthesized from 2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-(4-methoxyphenyl)pentanoic acid using standard conditions for the methoxy group hydrolysis (concentrated aqueous hydrochloric acid at reflux under argon for 24 h).

EXAMPLE 15

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-[4-(trifluoromethoxy)phenyl]-pentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 16

2-[(6-aminopyridin-3-yl)methyl]-5-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 17

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-tetrahydrothien-2-ylpentanoic acid was synthesised according to the procedure for Example 1, starting from 3-thien-2-ylpropanal.

EXAMPLE 18

2-[(6-aminopyridin-3-yl)methyl]-5-[3-(hydroxymethyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from 1-iodo-3-{[(4-methoxybenzyl)oxy]methyl}benzene. 1-iodo-3-{[(4-methoxybenzyl)oxy]methyl}benzene was synthesized from (3-iodophenyl)methanol using standard procedures.

EXAMPLE 19

2-[(6-aminopyridin-3-yl)methyl]-5-[2-(2,4-dichlorophenoxy)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 20

2-[(6-aminopyridin-3-yl)methyl]-5-(3,5-dimethylphenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 21

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-(4-propylphenyl)pentanoic acid was synthesised according to the procedure for Example 1.

EXAMPLE 22

2-[(6-aminopyridin-3-yl)methyl]-5-(4-benzylphenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1 starting from (4-iodophenyl)(phenyl)methanone.

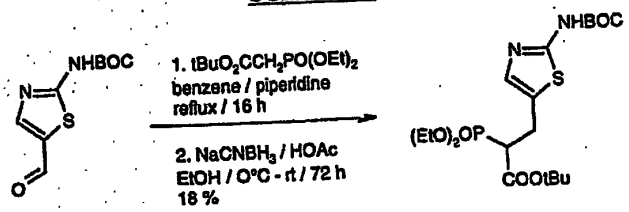
EXAMPLE 23

2-[(2-Amino-1,3-thiazol-5-yl)methyl]-3-mercapto-5-phenylpentanoic acid was synthesised according to the procedure for Example 1 starting from *tert*-butyl 3-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-5-yl}-2-(diethoxyphosphoryl)propanoate. *Tert*-butyl 3-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-5-yl}-2-(diethoxyphosphoryl)propanoate was synthesised as shown in Scheme 1.

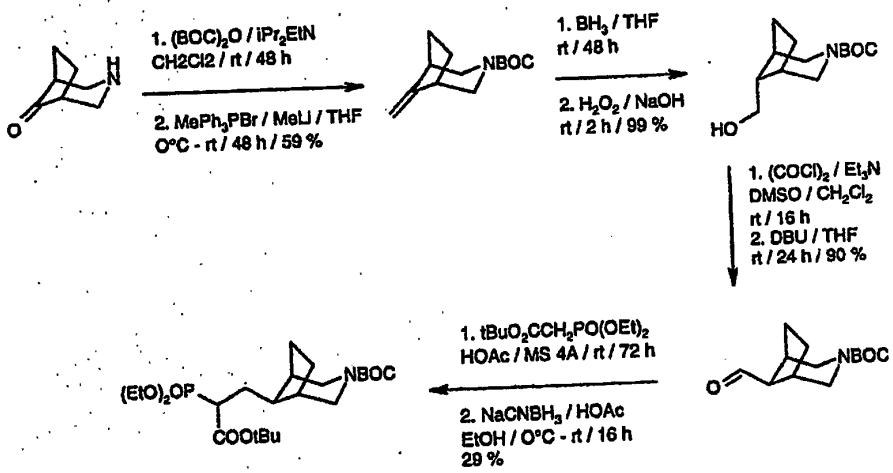
EXAMPLE 24

2-(3-azabicyclo[3.2.1]oct-8-ylmethyl)-3-mercapto-5-phenylpentanoic acid was synthesised according to the procedure for Example 1 starting from *tert*-butyl 8-[3-*tert*-butoxy-2-(diethoxyphosphoryl)-3-oxopropyl]-3-azabicyclo[3.2.1]octane-3-carboxylate. *Tert*-butyl 8-[3-*tert*-butoxy-2-(diethoxyphosphoryl)-3-oxopropyl]-3-azabicyclo[3.2.1]octane-3-carboxylate was synthesised as shown in Scheme 2.

SCHEME 1



SCHEME 2



Abbreviations

DMF = dimethylformamide

EtOAc = ethyl acetate

h = hour

HOAc = acetic acid

Me = methyl

MeOH = methanol

min = minutes

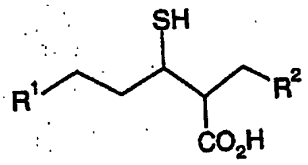
rt = room temperature

TFA = trifluoroacetic acid

THF = tetrahydrofuran

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 is phenyl {optionally substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano or hydroxy), C_{1-4} alkoxy, CF_3, OCF_3, methylenedioxy, $C(O)NH_2$, $S(O)_2NH_2$ or phenyl (itself optionally substituted by halogen)}, pyridinyl or tetrahydrothienyl;

R^2 is aminopyridinyl, aminothiazolyl or 3-azabicyclo[3.2.1]octyl;

provided that when R^1 is 6-aminopyridin-3-yl then R^2 is substituted phenyl, pyridinyl or tetrahydrothienyl;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

2. A compound of formula (I) as claimed in claim 1 wherein R^1 is phenyl {substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano or hydroxy), C_{1-4} alkoxy, CF_3 or methylenedioxy} or tetrahydrothiophenyl.

3. A compound of formula (I) as claimed in claim 1, 2 or 3 wherein R^2 is 6-aminopyridin-3-yl, 2-aminothiazol-5-yl or 3-azabicyclo[3.2.1]oct-8-yl.

4. A compound of formula (I) as claimed in claim 1, 2 or 3 wherein R^2 is 6-aminopyridin-3-yl.

5. Processes as herein described for preparating a compound of formula (I).

6. A pharmaceutical formulation containing a compound according to any one of claims 1 to 4 as active ingredient in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

7. The use of a compound as claimed in claim 1 in therapy.

8. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the inhibition of carboxypeptidase U.

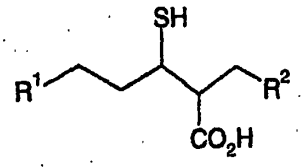
9. A method for treatment or prophylaxis of conditions where inhibition of carboxypeptidase U is beneficial, comprising administering to a mammal, including man, in need of such treatment an effective amount of a compound as claimed in claim 1.

10. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions where inhibition of carboxypeptidase U is beneficial, comprising a compound as claimed in claim 1 in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

ABSTRACT

CHEMICAL COMPOUNDS

The present invention concerns compounds of formula (I), and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts,



(I)

which compounds inhibit carboxypeptidase U and thus can be used in the prevention and treatment of diseases where inhibition of carboxypeptidase U is beneficial. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.